

Pharmaceuticals and Medical Devices Safety Information

No. 252 November 2008

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. PMDSI is available on the Pharmaceuticals and Medical Devices Agency website (<http://www.pmda.go.jp/english/index.html>) and on the MHLW website (<http://www.mhlw.go.jp/>, Japanese only).

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*This translation of the original Japanese text is for information purpose only
(in the event of inconsistency, the Japanese text shall prevail).*

Pharmaceuticals and Medical Devices Safety Information No. 252 November 2008

Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare, Japan

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	Hypermagnesaemia associated with magnesium oxide	<i>P</i> <i>C</i>	MHLW has alerted healthcare providers regarding the onset of hypermagnesaemia associated with magnesium oxide by describing “hypermagnesaemia” in the “Adverse Reactions” section of package inserts. Recently, as a result of organizing and investigating the reports of adverse reactions associated with magnesium oxide, on September 19, 2008, MHLW requested relevant pharmaceutical companies to revise PRECAUTIONS of the package inserts to provide additional alert about the onset of “hypermagnesaemia” such as by periodically measuring serum magnesium concentrations during the long-term administration of magnesium oxide. The content of these safety measures is described hereinafter.	3
2	Azelidipine	<i>P</i> <i>C</i>	Presents contents of revisions and summary of cases that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification dated September 19, 2008.	6
3	(1) Bromocriptin Mesilate (and 13 others) (2) Ureteral Stent		Revision of PRECAUTIONS (No. 201)	10
4	Products subject to Early Post-marketing Phase Vigilance		Lists products subject to Early Post-marketing Phase Vigilance as of November 1, 2008.	19

D: Distribution of Dear Healthcare Professional Letters *P*: Revision of PRECAUTIONS *C*: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, they are obligated to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

Hypermagnesaemia associated with magnesium oxide

Active Ingredient	Active ingredient	Brand name (name of company)
Brand Name (name of company)	Magnesium oxide	Magnesium oxide (Maruishi Pharmaceutical Co., Ltd.)etc.
Therapeutic Category	Antacids	
Indications	<ul style="list-style-type: none"> <input type="radio"/> Improvement of antacid action and symptoms in the following diseases Gastric ulcer, duodenal ulcer, gastritis (including acute and chronic gastritis and drug-induced gastritis), upper gastrointestinal dysfunction (including anorexia nervosa, so-called gastroptosis, and hyperchylia) <input type="radio"/> Constipation <input type="radio"/> Prophylaxis of calcium oxalate urolithiasis 	

1. Introduction

MHLW has alerted healthcare providers regarding the onset of hypermagnesaemia associated with magnesium oxide by describing “hypermagnesaemia” in the “Adverse Reactions” section of package inserts. Recently, as a result of organizing and investigating the reports of adverse reactions associated with magnesium oxide, on September 19, 2008, MHLW requested relevant pharmaceutical companies to revise PRECAUTIONS of the package inserts to provide additional alert about the onset of “hypermagnesaemia” such as by periodically measuring serum magnesium concentrations etc. during the long-term administration of magnesium oxide. The content of these safety measures is described hereinafter.

2. Onset conditions etc. of hypermagnesaemia

Magnesium oxide has been widely used as a laxative and as an antacid since 1950, and the number of patients treated with magnesium oxide for a year estimated by relevant pharmaceutical companies is approximately 45 million (2005).

The experts reviewed 15 cases of hypermagnesaemia (two fatal cases) reported from April 2005 to August 2008 for which a causality to magnesium oxide could not be denied. The results showed that there were cases in which the drug was assumed to have been chronically administered over the long-term to patients complicated by such as schizophrenia and dementia (see the table below), and cases which resulted in serious outcomes without realizing the symptoms were associated with hypermagnesaemia. Therefore, MHLW requested relevant pharmaceutical companies to add new sections “Important Precautions” and “Clinically Significant Adverse Reactions” in the PRECAUTIONS section of the package inserts, to describe “hypermagnesaemia” and a description of its initial symptoms etc. in the “Clinically Significant Adverse Reactions” section, and to explain in the “Important Precautions” section that serum magnesium concentrations should be periodically measured especially for the case in which the drug is administered over the long-term.

Healthcare providers should take further cares to ensure that they should adequately look out for the initial symptoms of hypermagnesaemia, and they should take further cares such as through periodically measuring serum magnesium concentrations and be able to take appropriate measures if any abnormalities are observed especially in the cases of long-term administration of magnesium oxide.

Number of cases according to treatment duration

Treatment duration	Less than 6 months	6 months and more	Description of "long-term administration" etc.	Unknown	Total
Number of events	2	1	6 (1)	6 (1)	15 (2)

(number of fatal cases)

«PRECAUTIONS (underlined parts are additions)»

[Important Precautions] Hypermagnesaemia may occur associated with this drug. Caution should be exercised particularly when the drug is administered over the long-term, such as by periodically measuring serum magnesium concentrations.

[Adverse Reactions (clinically significant adverse reactions)] Hypermagnesaemia: Hypermagnesaemia may occur associated with the administration of this drug, potentially resulting in respiratory depression, consciousness disturbed, arrhythmia, and cardiac arrest.
Caution should be paid to the onset of symptoms such as nausea, vomiting, thirst, blood pressure decreased, bradycardia, flushed skin, muscular weakness, and somnolence, and patients should be carefully monitored, such as by measuring serum magnesium concentrations. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Constipation (Hyperthyroidism, dementia)	2.0 g Unknown	<p>Hypermagnesaemia</p> <p>The patient was administered this drug to treat constipation while admitted to an institution for dementia.</p> <p>The patient suddenly developed massive diarrhoea, and was transported by the ambulance due to loss of consciousness. Shock and respiratory arrest were observed, and intratracheal intubation and artificial respiration were started. Serum magnesium level was high at 17.0 mg/dL. A calcium preparation was administered and acute haemodialysis (HD) was performed to restore shock.</p> <p>Although serum magnesium level gradually decreased, the patient got complication of sepsis. Bacteria were detected in ascites.</p> <p>Although intestinal necrosis was suspected, the patient died before performing surgery.</p>
Concomitant medications: None				

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 90s	Unknown (Chronic renal impairment)	1.5 g Description of “long-term administration”.*	<p>Hypermagnesaemia</p> <p>Although a nearby doctor made regular house calls to the patient (this drug was administered), the patient could walk on her own and showed no signs of dementia.</p> <p>9 days before discontinuation: The patient developed appetite impaired.</p> <p>3 days before discontinuation: The patient had no energy and was unable to respond to questions.</p> <p>Day of discontinuation: There was further depressed level of consciousness and the patient was referred to this hospital. At the time of hospitalization, the patient’s level of consciousness was JCSII-20, blood pressure was 96/60 mmHg, there was flushed face, and electrocardiogram showed sinus bradycardia (38/min.). Levels of BUN and serum creatinine were 53.9 mg/dL and 2.17 mg/dL, respectively. Respiratory depression was suspected from arterial blood gas analysis of PO₂ 76.3 mmHg and PCO₂ 51.8 mmHg. The patient was continuously administered the drug over the long-term, and as hypermagnesaemia was suspected by the findings, haemodialysis was started from the same day. At time of hospitalization, serum magnesium level was 6.1 mg/dL (average level: 1.7–2.6 mg/dL). Administration of this drug was discontinued.</p> <p>Later, serum magnesium level dropped to 2.4 mg/dL due to 3 times of haemodialysis. Serum creatinine level was reduced to 1.3 mg/dL following dialysis, and the level was maintained thereafter.</p> <p>6 days after discontinuation: Abnormal findings such as disturbed consciousness completely disappeared.</p>
Concomitant medications: None				

* Long-term administration for at least more than 1 year is presumed.

Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the PRECAUTIONS section of package inserts of drugs that have been revised in accordance with the Notification dated September 19, 2008.

1 Azelnidipine

Brand Name (name of company)	CALBLOCK Tablets 8 mg and 16 mg (Daiichi-Sankyo Co., Ltd.)
Therapeutic Category	Antihypertensives
Indications	Hypertension

《PRECAUTIONS (underlined parts are additions)》

**[Adverse Reactions
(clinically significant
adverse reactions)]**

Hepatic function disorder, jaundice: Hepatic function disorder with elevations of AST (GOT), ALT (GPT), γ -GTP, and jaundice may occur. Patients should be closely monitored and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

<Reference Information>

The number of reported adverse reaction cases in about the last 3 years (April 1, 2005 to July 8, 2008) (events for which a causality to the drug could not be denied)

- Hepatic function disorder, jaundice: 8 cases (of which 1 had a fatal case)

The number of patients treated with Azelnidipine for a year estimated by MAH: approximately 450000 (2007)

Marketed in Japan in: May 2003

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 80s	Hypertension (hyperlipidaemia, hyperuricaemia, hypothyroidism)	8 mg 82 days	<p>Hepatitis fulminant</p> <p>Approx. 5 years and 8 months before administration: The patient received her first medical examination. Hypertension was confirmed (period of onset: unknown).</p> <p>On day 1 of administration: Administration of 8 mg/day of this drug was started to treat hypertension.</p> <p>On day 29 of administration: The patient was examined as an outpatient. She had no particular complaints.</p> <p>On day 57 of administration: The patient was examined as an outpatient. She had no particular complaints.</p> <p>On day 82 of administration (day of discontinuation): The patient was examined for malaise and anasarca.</p>

				<p>AST (GOT) 953 IU/L, ALT (GPT) 472 IU/L, Al-P 1111 IU/L, LDH 767 IU/L, γ-GTP 659 IU/L. Severe liver disorder was confirmed.</p> <p>Echocardiogram showed no problems. Ascites, pericardial fluid, and pleural effusion were confirmed and the patient was hospitalized. Disturbed consciousness was confirmed.</p> <p>The patient was negative for both the hepatitis B virus and the hepatitis C virus.</p> <p>Administration of this drug and all concomitant medications were discontinued.</p> <p>Administration of glycyrrhizin/glycine/cysteine was started.</p> <p>1 day after discontinuation: Ammonia was 172 μg/dL, grade 3 hepatic encephalopathy.</p> <p>2 days after discontinuation: Prothrombin activity 28%, total bilirubin 5.3 mg/dL. Administration of an amino-acid preparation for hepatic failure was started.</p> <p>3 days after discontinuation: Prothrombin activity 18%, ammonia 272 μg/dL, and total bilirubin 8.1 mg/dL. Antinuclear antibody level < below 1:40 (negative). Plasma exchange was conducted.</p> <p>4 days after discontinuation: Prothrombin activity 15%, ammonia 115 μg/dL, total bilirubin 6.1 mg/dL. Plasma exchange was conducted. Administration of a liver extract and flavin adenine dinucleotide, and adrenal corticosteroids was started.</p> <p>5 days after discontinuation: Prothrombin activity 26%, ammonia 204 μg/dL, and total bilirubin 5.2 mg/dL. Plasma exchange was conducted.</p> <p>7 days after discontinuation: Prothrombin activity 4%, ammonia 556 μg/dL, and total bilirubin 9.4 mg/dL. Reexamination for various hepatitis viruses was negative. The patient's general conditions did not improve and she died.</p>
Concomitant medications: fluvastatin sodium, allopurinol, levothyroxine sodium hydrate				

Clinical Laboratory Values

	175 days before administration	On day 82 of administration (day of discontinuation)	2 days after discontinuation	3 days after discontinuation	4 days after discontinuation	7 days after discontinuation
AST (GOT) (IU/L)	28	953	928	3108	2535	229
ALT (GPT) (IU/L)	20	472	404	1323	1300	175
Al-P (IU/L)	261	1111	—	—	—	—
LDH (IU/L)	253	767	—	—	—	668
γ -GTP (IU/L)	14	659	624	702	—	—
Total bilirubin (mg/dL)	—	4.4	5.3	8.1	6.1	9.4
BUN (mg/dL)	14	22	40	44	41	23
Cr (mg/dL)	0.82	1.55	2.57	2.95	2.97	2.52
Ammonia (μ g/dL)	—	—	—	272	115	556
PT activity (%)	—	—	28	18	15	4
PT-INR	—	—	2.49	3.87	4.69	9.99

AST: Aspartate Aminotransferase
 ALT: Alanine Aminotransferase
 Al-P: Alkaline Phosphatase
 LDH: Lactate Dehydrogenase
 γ-GTP: γ-Glutamyltranspeptidase

BUN: Blood Urea Nitrogen
 Cr: Creatinine
 PT activity: Prothrombin Activity (%)
 PT-INR: Prothrombin Time-International Normalized Ratio

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Hypertension (cervical spondylosis)	16 mg 27 days	<p>Liver disorder Approx. 12 years before administration: Administration of manidipine hydrochloride was started at another hospital to treat hypertension.</p> <p>Approx. 7 years before administration: The patient received her first medical examination at this hospital.</p> <p>On day 1 of administration: Antihypertensive drug was switched from manidipine hydrochloride to 16 mg/day of this drug due to poorly-controlled blood pressure.</p> <p>On day 23 of administration: Brown urine and general malaise developed.</p> <p>On day 26 of administration: As slight conjunctiva bulbi colouring yellow was confirmed, a blood test was done. Liver disorder was confirmed with AST (GOT) 193 IU/L, ALT (GPT) 422 IU/L, and total bilirubin 2.7 mg/dL.</p> <p>On day 27 of administration (day of discontinuation): The patient was referred to another hospital and hospitalized. Although acute viral hepatitis was suspected, HCV antibodies and HBs antigens were both negative. As eosinophil count was high at 29%, drug-induced hepatic disorder was suspected and administration of this drug, mecobalamin, and eperisone hydrochloride were discontinued (the patient had been taking mecobalamin and eperisone hydrochloride for approximately 3 years).</p> <p>6 days after discontinuation: AST (GOT) 29 IU/L, ALT (GPT) 98 IU/L, total bilirubin 0.5 mg/dL.</p> <p>7 days after discontinuation: As liver function test values improved, the patient was discharged from the hospital. The antihypertensive agent was switched to valsartan 80 mg/day.</p> <p>Approx. 1 month after discontinuation: The patient was recovered from hepatic disorder.</p>
Concomitant medications: mecobalamin, eperisone hydrochloride				

Clinical Laboratory Values

	57 days before administration	On day 26 of Administration	On day 27 of admin. (day of discontinuation)	2 days after discontinuation	6 days after discontinuation
AST (GOT) (IU/L)	22	193	77	76	29
ALT (GPT) (IU/L)	16	422	306	194	98
Al-P (IU/L)	—	—	940	674	555
γ -GTP (IU/L)	41	789	750	549	396
Total bilirubin (mg/dL)	—	2.7	1.1	0.8	0.5
Direct bilirubin (mg/dL)	—	2.0	—	—	—

AST: Asparate Aminotransferase
ALT: Alanine Aminotransferase

Al-P: Alkaline Phosphatase
 γ -GTP: γ -Glutamyltranspeptidase

Revision of PRECAUTIONS (No. 201)

(1) Drugs

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of drugs that have been revised according to the Notifications dated September 19, 2008 (excluding those presented in “1. Hypermagnesaemia associated with magnesium oxide” and “2. Important Safety Information” of this Bulletin).

1 <Antiparkinsonian agents>

1 Bromocriptin Mesilate

[Brand Name]

Parlodel 2.5 mg
(Novartis Pharma K.K.), and others

[Contraindications]

Patients with cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis etc. confirmed by echocardiogram, and patients with a history of such diseases.

[Important Precautions]

Impulse-control disorders such as pathological gambling (a state of continuous gambling despite bringing about socially detrimental results such as the destruction of the individual's life), increased libido and hypersexuality have been reported in patients with Parkinson's disease receiving levodopa or dopamine receptor agonist. If such symptoms are observed, appropriate measures such as reducing or discontinuing administration should be taken.

[Adverse Reactions (clinically significant adverse reactions)]

Pleurisy, pericarditis, pleural fibrosis, pulmonary fibrosis: Pleural effusion, pericardial fluid, pleurisy, pericarditis, pleural fibrosis, pulmonary fibrosis may occur. If chest pain and respiratory symptoms etc. are observed, chest X-ray examination should be promptly conducted. If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken. In particular, the risk of onset may increase in patients administered a high dose over the long-term.

Cardiac valvulopathy: Since cardiac valvulopathy may occur, patients should be carefully monitored. If development and/ or aggravation of cardiac murmur is observed, chest X-ray examination or echocardiography etc. should be promptly performed. If cardiac valve leaflet thickening, cardiac valve motion restriction or associated cardiac valve lesion such as stenosis are observed, administration of this drug should be discontinued and appropriate measures should be taken. In particular, the risk of onset may increase in patients administered a high dose over the long-term.

Retroperitoneal fibrosis: Retroperitoneal fibrosis has been reported to occur. Patients should be carefully monitored and if back pain, oedema lower limb, and renal impairment etc. are observed, administration should be discontinued and appropriate measures should be taken. In particular, the risk of onset may increase in patients administered a high dose over the long-term.

2 <Antiparkinsonian agents>
Cabergoline

[Brand Name] CABASER Tab. 0.25 mg and 1.0 mg
(Pfizer Japan Inc.), and others

[Important Precautions] Impulse-control disorders such as pathological gambling (a state of continuous gambling despite bringing about socially detrimental results such as the destruction of the individual's life), increased libido and hypersexuality have been reported in patients with Parkinson's disease receiving levodopa or dopamine receptor agonist. If such symptoms are observed, appropriate measures such as reducing or discontinuing administration should be taken.

[Adverse Reactions (clinically significant adverse reactions)] **Retroperitoneal fibrosis:** Retroperitoneal fibrosis has been reported to occur. Patients should be carefully monitored and if back pain, oedema lower limb, and renal impairment etc. are observed, administration should be discontinued and appropriate measures should be taken.

3 <Antiparkinsonian agents>
Talipexole Hydrochloride, Pramipexole Hydrochloride Hydrate, Levodopa, Levodopa-Carbidopa, Levodopa-Benserazide Hydrochloride, Ropinirole Hydrochloride

[Brand Name] Domin Tablets 0.4 (Nippon Boehringer Ingelheim Co., Ltd.)
BI·Sifrol Tablets 0.125 mg and 0.5 mg (Nippon Boehringer Ingelheim Co., Ltd.)
DOPASOL TABLETS (Daiichi-Sankyo Co., Ltd.), DOPARL Fine Granules 99.5%, DOPARL Tablets 200 (Kyowa Hakko Kirin Co., Ltd.), DOPASTON INJECTION (OHARA Pharmaceutical Co., Ltd.), and others
NEODOPASTON TABLETS 100 mg and 250 mg (Daiichi-Sankyo Co., Ltd.), Menesit Tablets-100 and -250 (Banyu Pharmaceutical Co., Ltd.), and others
EC-DOPARL Tablets (Kyowa Hakko Kirin Co., Ltd.), NEODOPASOL TABLETS (Daiichi Sankyo Co., Ltd.), MADOPAR Tablets (Chugai Pharmaceutical Co., Ltd.)
ReQuip Tablets 0.25 mg, 1 mg, and 2 mg (GlaxoSmithKline K.K.)

[Important Precautions] Impulse-control disorders such as pathological gambling (a state of continuous gambling despite bringing about socially detrimental results such as the destruction of the individual's life), increased libido and hypersexuality have been reported in patients with Parkinson's disease receiving levodopa or dopamine receptor agonist. If such symptoms are observed, appropriate measures such as reducing or discontinuing administration should be taken.

4 <Antiparkinsonian agents>
Pergolide Mesilate

[Brand Name] Permax Tablets 50 µg and 250 µg
(Eli Lilly Japan K.K.), and others

[Important Precautions] Impulse-control disorders such as pathological gambling (a state of continuous gambling despite bringing about socially detrimental results such as the destruction of the individual's life), increased libido and hypersexuality have been reported in patients with Parkinson's disease receiving levodopa or dopamine receptor agonist. If such symptoms are observed, appropriate measures such as reducing or discontinuing administration should be taken.

[Adverse Reactions (clinically significant adverse reactions)] **Retroperitoneal fibrosis:** Retroperitoneal fibrosis has been reported to occur. Patients should be carefully monitored and if back pain, oedema lower limb, and renal impairment etc. are observed, administration should be discontinued and appropriate measures should be taken.

5 <Psychotropics>
Modafinil

[Brand Name]	Modiodal Tablets 100 mg (Alfresa Pharma Corporation)
[Careful Administration]	Patients with <u>depression, mania, and other mental conditions, or patients with a history of such diseases.</u>
[Important Precautions]	<u>Psychiatric symptoms such as hallucination, delusion, and suicidal ideation have been reported even in patients without depression, mania, and other mental conditions, or patients without a history of such diseases. If these symptoms are observed, discontinuation of administration should be considered.</u>

6 <Antihypertensives>
Carvedilol

[Brand Name]	ARTIST TABLETS 1.25 mg, 2.5 mg, 10 mg, and 20 mg (Daiichi-Sankyo Co., Ltd.), and others
[Important Precautions]	If the drug is administered over the long-term, cardiac function tests (pulse rate, blood pressure, electrocardiogram, and X-ray etc.) should be periodically performed. <u>As well, the cases of shock have been reported</u> if bradycardia and hypotension develop, patients should be <u>carefully</u> monitored and administration should be reduced or discontinued. Atropine, dobutamine, isoproterenol, and adrenaline, etc. should be used as necessary. In addition, caution should be exercised for hepatic function, renal function, and haemogram.
[Adverse Reactions (clinically significant adverse reactions)]	The following clinically significant adverse reactions to the cardiovascular system may occur. Cardiac function tests (pulse rate, blood pressure, electrocardiogram, and X-ray etc.) should be periodically performed. If such symptoms are observed, appropriate measures such as reduction or discontinuation of administration should be taken. Severe bradycardia <u>Shock</u> Atrioventricular block complete Cardiac failure Cardiac arrest

7 <Cardiovascular agents-Miscellaneous>
Dihydroergotoxine Mesilate

[Brand Name]	Hydergine Sublingual Tablets 1 mg and Hydergine Tablets 2 mg (Novartis Pharma K.K.), and others	
[Contraindications]	<table border="1"><tr><td><u>Patients with cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis etc. confirmed by echocardiogram, and patients with a history of such diseases.</u></td></tr></table>	<u>Patients with cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis etc. confirmed by echocardiogram, and patients with a history of such diseases.</u>
<u>Patients with cardiac valve leaflet thickening, cardiac valve motion restriction, and associated cardiac valve lesions such as stenosis etc. confirmed by echocardiogram, and patients with a history of such diseases.</u>		
[Adverse Reactions (clinically significant adverse reactions)]	<u>Retroperitoneal fibrosis:</u> <u>Retroperitoneal fibrosis has been reported to occur. Patients should be carefully monitored and if back pain, oedema lower limb, and renal impairment etc. are observed, administration should be discontinued and appropriate measures should be taken.</u>	

8 Estradiol Preparations (oral dosage form, injectable dosage form) (indications include climacteric disturbance) Estriol Preparations (indications include climacteric disturbance) Androgen/Estrogen Combinations Preparation

[Brand Name]	Julina Tablets 0.5 mg (Bayer Yakuhin, Ltd.), OVAHORMON AQUEOUS SUSPENSION 0.2 and 1, OVAHORMON DEPOT 5 mg (Aska Pharmaceutical Co., Ltd.), Progynon-Depot intramuscular injection 10 mg (Fuji Pharma Co., Ltd.), and others ESTRIEL Tablets 100 γ , 0.5 mg, and 1 mg, ESTRIEL DEPOT 10 mg for Inj. (Mochida Pharmaceutical Co., Ltd.), HOLIN TABLETS 1 mg, HOLIN DEPOT (Aska Pharmaceutical Co., Ltd.), and others Primodian-Depot intramuscular injection (Fuji Pharma Co., Ltd.), BOTHERMON DEPOT 50 mg, BOTHERMON INJECTION 5.0 mg (Aska Pharmaceutical Co., Ltd.), and others
[Important Precautions]	Medical histories including histories of diseases and genetic predisposition should be taken, and breast examination and gynecological examination should be performed before initiating therapy with this drug. After starting administration, periodic breast examinations and gynecological examinations should be performed (<u>including cytology of the endometrium and endometrial thickness measurement by pelvic ultrasonography for women (intact uterus)</u>).
[Other Precautions]	Hormone replacement therapy (HRT) and the risk of breast cancer 1) A randomized clinical trial in postmenopausal women conducted in the United States [<u>Women's Health Initiative (WHI) Study</u>] reported that the risk of breast cancer increased significantly higher in women receiving CE/MPA compared to women receiving placebo (Hazard Ratio: 1.24). The sub study for women treated post-hysterectomy reported that the risk of breast cancer didn't increase significantly higher in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 0.80). 2) A result of epidemiologic investigation conducted in the United Kingdom [<u>Million Women Study (MWS)</u>] reported that the risk of breast cancer increased significantly higher in women receiving CE/MPA compared to women receiving placebo (2.00 times). It was reported that this risk increased the longer the period of concomitant administration became (less than 1 year: 1.45 times; 1–4 years: 1.74 times; 5–9 years: 2.17 times; more than 10 years: 2.31 times). HRT and the risks of coronary heart disease <u>WHI study</u> reported that the risk of coronary artery disease relatively increased higher in women receiving CE/MPA compared to women receiving placebo, especially, increased significantly after receiving 1 year (Hazard Ratio: 1.81). The sub study for women treated post-hysterectomy reported that the risk of coronary artery disease didn't increase significantly in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 0.91). HRT and the risks of stroke <u>WHI study</u> reported that the risk of stroke (mainly cerebral infarction) relatively increased higher in women receiving CE/MPA compared to women receiving placebo (Hazard Ratio: 1.31). The sub study for women treated post-hysterectomy reported that the risk of stroke (mainly cerebral infarction) increased significantly higher in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 1.37). HRT and the risks of <u>dementia</u> A randomized clinical trial in postmenopausal women conducted in the United States [<u>WHI Memory Study (WHIMS)</u>] for postmenopausal women 65 years of age and older reported that the risk of <u>dementia</u> including Alzheimer's disease increased significantly higher in women receiving CE/MPA compared to women receiving placebo (Hazard Ratio: 2.05). The sub study for women treated post-hysterectomy reported that the risk of

dementia increased relatively high but not significant in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 1.49).

HRT and the risks of ovarian cancer

- 1) Epidemiological studies reported that the risk of ovarian cancer increased in postmenopausal women who used estrogens for a long period compared to control group.
- 2) WHI study reported that the risk of ovarian cancer didn't increase significantly in women receiving CE/MPA compared to women receiving placebo, but increased relatively high (Hazard Ratio: 1.58).

HRT and the risks of endometrial cancer

Epidemiological studies reported that the risk of endometrial cancer increased in postmenopausal women who used estrogens for a long period compared to control group (more than approximately 1 year). It was reported that this risk increases in proportion to the period of use (2.8 times for 1–5 years; 9.5 times for more than 10 years), and that the risk is suppressed by the concomitant administration of a progesterone preparation (at 0.8 times risk compared to the women in the control group).

HRT and the risks of disease gallbladder

A randomized clinical trial in postmenopausal women conducted in the United States [Women's Health Initiative (WHI) Study] reported that the risk of gallbladder disease increased significantly higher in women receiving CE/MPA compared to women receiving placebo (Hazard Ratio: 1.59). The sub study for women treated gallbladder disease reported that the risk of breast cancer increased significantly higher in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 1.67).

<Estrogen and progesterone preparations>

9 Estradiol Preparations (external dosage form) (indications include climacteric disturbance)

[Brand Name]

ESTRADERM Plaster 0.72 mg (Kissei Pharmaceutical Co., Ltd.), ESTRANA TAPE 0.72 mg (Hisamitsu Pharmaceutical Co., Inc.), DIVIGEL 1 mg (Pola Pharma Inc.), FEMIEST 2.17 mg and 4.33 mg (Yakult Honsha Co., Ltd.), l'estrogele 0.06% (Shiseido Co., Ltd.), and others

[Important Precautions]

Medical histories including histories of diseases and genetic predisposition should be taken, and breast examination and gynecological examination should be performed before initiating therapy with this drug. After starting administration, periodic breast examinations and gynecological examinations should be performed (including cytology of the endometrium and endometrial thickness measurement by pelvic ultrasonography for women (intact uterus)).

[Other Precautions]

Hormone replacement therapy (HRT) and the risk of breast cancer

- 1) A randomized clinical trial in postmenopausal women conducted in the United States [Women's Health Initiative (WHI) Study] reported that the risk of breast cancer increased significantly higher in women receiving CE/MPA compared to women receiving placebo (Hazard Ratio: 1.24). The sub study for women treated post-hysterectomy reported that the risk of breast cancer didn't increase significantly higher in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 0.80).
- 2) A result of epidemiologic investigation conducted in the United Kingdom [Million Women Study (MWS)] reported that the risk of breast cancer increased significantly higher in women receiving CE/MPA compared to women receiving placebo (2.00 times). It was reported that this risk increased the longer the period of concomitant administration became (less than 1 year: 1.45 times; 1–4 years: 1.74 times; 5–9 years: 2.17 times; more than 10 years: 2.31 times).

HRT and the risks of coronary heart disease

WHI study reported that the risk of coronary artery disease relatively increased higher in women receiving CE/MPA compared to women receiving placebo, especially, increased significantly after receiving 1 year

(Hazard Ratio: 1.81). The sub study for women treated post-hysterectomy reported that the risk of coronary artery disease didn't increase significantly in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 0.91).

HRT and the risks of stroke

WHI study reported that the risk of stroke (mainly cerebral infarction) relatively increased higher in women receiving CE/MPA compared to women receiving placebo (Hazard Ratio: 1.31). The sub study for women treated post-hysterectomy reported that the risk of stroke (mainly cerebral infarction) increased significantly higher in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 1.37).

HRT and the risks of dementia

A randomized clinical trial in postmenopausal women conducted in the United States [WHI Memory Study (WHIMS)] for postmenopausal women 65 years of age and older reported that the risk of dementia including Alzheimer's disease increased significantly higher in women receiving CE/MPA compared to women receiving placebo (Hazard Ratio: 2.05). The sub study for women treated post-hysterectomy reported that the risk of dementia increased relatively high but not significant in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 1.49).

HRT and the risks of ovarian cancer

- 1) Epidemiological studies reported that the risk of ovarian cancer increased in postmenopausal women who used estrogens for a long period compared to control group.
- 2) WHI study reported that the risk of ovarian cancer didn't increase significantly in women receiving CE/MPA compared to women receiving placebo, but increased relatively high (Hazard Ratio: 1.58)..

HRT and the risks of endometrial cancer

Epidemiological studies reported that the risk of endometrial cancer increased in postmenopausal women who used estrogens for a long period compared to control group (more than approximately 1 year). It was reported that this risk increases in proportion to the period of use (2.8 times for 1–5 years; 9.5 times for more than 10 years), and that the risk is suppressed by the concomitant administration of a progesterone preparation (at 0.8 times higher risk compared to the women in the control group).

HRT and the risks of disease gallbladder

A randomized clinical trial in postmenopausal women conducted in the United States [Women's Health Initiative (WHI) Study] reported that the risk of gallbladder disease increased significantly higher in women receiving CE/MPA compared to women receiving placebo (Hazard Ratio: 1.59). The sub study for women treated gallbladder disease reported that the risk of breast cancer increased significantly higher in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 1.67).

10 <Estrogen and progesterone preparations> Conjugated Estrogens

[Brand Name]

PREMARIN TABLETS 0.625 mg
(Wyeth K.K.)

[Important Precautions]

Medical histories including histories of diseases and genetic predisposition should be taken, and breast examination and gynecological examination should be performed before initiating therapy with this drug. After starting administration, periodic breast examinations and gynecological examinations should be performed (including cytology of the endometrium and endometrial thickness measurement by pelvic ultrasonography for women (intact uterus)).

[Other Precautions]

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- 1) A randomized clinical trial in postmenopausal women conducted in the United States [Women's Health Initiative (WHI) Study] reported that the risk of breast cancer increased significantly higher in women receiving

CE/MPA compared to women receiving placebo (Hazard Ratio: 1.24). The sub study for women treated post-hysterectomy reported that the risk of breast cancer didn't increase significantly higher in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 0.80).

- 2) A result of epidemiologic investigation conducted in the United Kingdom [Million Women Study (MWS)] reported that the risk of breast cancer increased significantly higher in women receiving CE/MPA compared to women receiving placebo (2.00 times). It was reported that this risk increased the longer the period of concomitant administration became (less than 1 year: 1.45 times; 1–4 years: 1.74 times; 5–9 years: 2.17 times; more than 10 years: 2.31 times).

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WHI study reported that the risk of coronary artery disease relatively increased higher in women receiving CE/MPA compared to women receiving placebo, especially, increased significantly after receiving 1 year (Hazard Ratio: 1.81). The sub study for women treated post-hysterectomy reported that the risk of coronary artery disease didn't increase significantly in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 0.91).

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HRT and the risks of endometrial cancer

Epidemiological studies reported that the risk of endometrial cancer increased in postmenopausal women who used estrogens for a long period compared to control group (more than approximately 1 year). It was reported that this risk increases in proportion to the period of use (2.8 times for 1–5 years; 9.5 times for more than 10 years), and that the risk is suppressed by the concomitant administration of a progesterone preparation (at 0.8 times higher risk compared to the women in the control group).

HRT and the risks of disease gallbladder

A randomized clinical trial in postmenopausal women conducted in the United States [Women's Health Initiative (WHI) Study] reported that the risk of gallbladder disease increased significantly higher in women receiving CE/MPA compared to women receiving placebo (Hazard Ratio: 1.59). The sub study for women treated gallbladder disease reported that the risk of breast cancer increased significantly higher in women receiving CE alone compared to women receiving placebo (Hazard Ratio: 1.67).

11 <Antineoplastics-Miscellaneous>
Bortezomib

[Brand Name] VELCADE Injection 3 mg
(Janssen Pharmaceutical K.K.)

[Adverse Reactions (clinically significant adverse reactions)] Ileus: Ileus may occur. Patients should be carefully monitored. If symptoms of anorexia, vomiting, constipation, and abdominal enlarged feeling are observed, appropriate measures should be taken.

12 <Acting mainly on gram-positive bacteria and mycoplasma>
Clarithromycin

[Brand Name] Klaricid Tablets 50 mg for Pediatric Use and 200 mg, Klaricid Dry Syrup 10% for Pediatric Use (Abbott Japan Co., Ltd.), Clarith tab. 50 for pediatric, and 200 Clarith dry syrup 10% for pediatric (Taisho Pharmaceutical Co., Ltd.), and others

[Adverse Reactions (clinically significant adverse reactions)] QT prolongation, ventricular tachycardia, (including Torsades de pointes), ventricular fibrillation: Since QT prolongation, ventricular tachycardia (including Torsades de pointes) and/or ventricular fibrillation may occur, patients should be closely monitored. If any abnormalities are observed, administration should be discontinued and appropriate therapeutic action taken. When using this product in patients with cardiac disorder (e.g., prolonged QT), pay special attention to adverse reactions.

13 <Acting mainly on mold>
Amphotericin B (injectable dosage form)

[Brand Name] AmBisome 50 mg for Intravenous Drip Infusion (Dainippon Sumitomo Pharma Co., Ltd.), FUNGIZONE 50 mg FOR INFUSION (Bristol-Myers K.K)

[Adverse Reactions (clinically significant adverse reactions)] Rhabdomyolysis: Rhabdomyolysis with hypokalaemia may occur. If myalgia, feeling of weakness, CK (CPK) increased, myoglobin blood increased, and urine myoglobin increased etc. are observed, administration should be discontinued and appropriate measures should be taken.

14 <Antibiotics-Miscellaneous>
Lansoprazole/Amoxicillin Hydrate/Clarithromycin

[Brand Name] LANSAP 400 and 800
(Takeda Pharmaceutical Company Limited)

[Adverse Reactions (clinically significant adverse reactions)] (Clarithromycin)
QT prolongation, ventricular tachycardia, (including Torsades de pointes), ventricular fibrillation: Since QT prolongation, ventricular tachycardia (including Torsades de pointes) and/or ventricular fibrillation may occur, patients should be closely monitored. If any abnormalities are observed, administration should be discontinued and appropriate therapeutic action taken. When using this product in patients with cardiac disorder (e.g., prolonged QT), pay special attention to adverse reactions.

(2) Medical Devices

This section presents details of revisions to the PRECAUTIONS section of package inserts and brand names of medical devices that have been revised according to the Notification dated October 6, 2008.

1 Ureteral Stent

[Brand Name] Integral Ureter Stent Set (Teleflex Medical), Ureteral Pigtail Stent Set (Kysmaq Co., Ltd.), Amplatz Ureteral Stent Sets Ultrathane (Cook Japan Inc.), Ureteral Stent, etc. (Goodtec. Co., Ltd.), Silicone KAIBA Sprint Catheter, etc. (Create Medic Co., Ltd.), Biosoft Duo Double Loop Ureteral Stents, etc. (Coloplast A/S), Ureteral catheter, etc. (Takai Hospital Supply Co., Ltd.), Urete-Jin Drain Catheter (Stent Type), etc. (Nippon Sherwood Medical Industries Ltd.), GYRUS ACMI Silitek Stent, etc. (Harada Corp.), Urecath, etc. (B. Braun Aesculap Japan Co., Ltd.), Nephrostomy Catheter (Fuji Systems Corp.), Polaris Ultra, etc. (Boston Scientific Japan K.K.), Bard Inlay Ureteral Stent Tri-Pak, etc. (Medicon, Inc.)

[Warning]

WARNING

If the patient has a history of pelvic operation and/or pelvic irradiation and has an indwelling ureteral stent over the long-term, an arterio-ureteral fistula may be formed between the urinary duct and aorta or iliac artery, with the potentiality of a result in massive bleeding during the replacement of the ureteral stent. Patients should be carefully monitored over time and if bleeding from the urinary tract is observed, pyelogram retrograde and angiogram etc. should be performed to make a diagnosis, and appropriate measures should be taken.

4

List of products subject to Early Post-marketing Phase Vigilance

(As of November 1, 2008)

Nonproprietary name ----- Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Tocilizumab (Genetical recombination) ----- Actemra for Intravenous Infusion 200 mg ^{*1}	Chugai Pharmaceutical Co., Ltd.	April 16, 2008
Varenicline Tartrate ----- Champix Tablets 0.5 mg and 1 mg	Pfizer Japan Inc.	May 8, 2008
— ----- Artcereb Irrigation and Perfusion Solution for Cerebrospinal Surgery	Otsuka Pharmaceutical Factory, Inc.	May 12, 2008
Thrombomodulin Alfa (Genetical recombination) ----- Recomodulin Inj.12800	Asahi Kasei Pharma Corporation	May 12, 2008
Human Serum Albumin (Genetical recombination) ----- Medway Injection 25% and 5%	Mitsubishi Tanabe Pharma Corporation	May 19, 2008
Tacrolimus Hydrate ----- Talymus Ophthalmic Suspension 0.1%	Senju Pharmaceutical Co., Ltd.	May 20, 2008
Fondaparinux Sodium ----- Arixtra Injection 1.5 mg and 2.5 mg ^{*2}	GlaxoSmithKline K.K.	May 20, 2008
Sitafloxacin Hydrate ----- Gracevit Tablets 50 mg, Gracevit Fine Granules 10%	Daiichi Sankyo Co., Ltd.	June 2, 2008
Sunitinib Malate ----- Sutent Capsule 12.5 mg	Pfizer Japan Inc.	June 13, 2008
Tocilizumab (Genetical recombination) ----- Actemra for Intravenous Infusion 80 mg and 400 mg	Chugai Pharmaceutical Co., Ltd.	June 13, 2008
Deferasirox ----- Exjade Dispersible Tablets 125 mg and 500 mg	Novartis Pharma K.K.	June 16, 2008
Adalimumab (Genetical recombination) ----- Humira Subcutaneous Injection 40 mg Syringe 0.8 mL	Abbott Japan Co., Ltd.	June 18, 2008
Irbesartan ----- Avapro Tablets 50 mg and 100 mg	Dainippon Sumitomo Pharma Co., Ltd.	July 1, 2008
Irbesartan ----- Irbetan Tablets 50 mg and 100 mg	Shionogi & Co., Ltd.	July 1, 2008
Famciclovir ----- Famvir Tab. 250 mg	Asahi Kasei Pharma Corporation	July 1, 2008
Raltegravir Potassium ----- Isentress Tablets 400 mg	Banyu Pharmaceutical Co., Ltd.	July 7, 2008
Norethisterone/Ethinylestradiol ----- Lunabell Tablets	Nobelpharma Co., Ltd.	July 8, 2008
Argatroban Hydrate ----- Slonnon HI Injection 10 mg/2 mL ^{*3}	Daiichi Sankyo Co., Ltd.	July 16, 2008

Argatroban Hydrate Novastan HI inj. 10 mg/2 mL ^{*3}	Mitsubishi Tanabe Pharma Corporation	July 16, 2008
Sapropterin Hydrochloride Biopten Granules 2.5% ^{*4}	Asubio Pharma Co., Ltd.	July 16, 2008
Sodium Risedronate Hydrate Actonel Tab. 17.5 mg ^{*5}	Ajinomoto Co., Inc.	July 16, 2008
Sodium Risedronate Hydrate Benet Tablets 17.5 mg ^{*5}	Takeda Pharmaceutical Company Limited	July 16, 2008
Diazoxide Aroglycem Capsules 25 mg	Schering-Plough K.K.	July 22, 2008
Yttrium (⁹⁰ Y) Ibritumomab Tiuxetan (Genetical recombination) Zevalin yttrium (⁹⁰ Y) injection	Bayer Yakuhin, Ltd.	August 4, 2008
Indium (¹¹¹ In) Ibritumomab Tiuxetan (Genetical recombination) Zevalin indium (¹¹¹ In) injection	Bayer Yakuhin, Ltd.	August 4, 2008
Levobupivacaine Hydrochloride POPSCAINE 0.75% inj. 75 mg/10 mL, POPSCAINE 0.75% inj. 150 mg/20 mL, POPSCAINE 0.25% inj. 25 mg/10 mL, POPSCAINE 0.25% inj. bag 250 mg/100 mL, POPSCAINE 0.75% inj. syringe 75 mg/10 mL, POPSCAINE 0.25% inj. syringe 25 mg/10 mL	Maruishi Pharmaceutical Co., Ltd.	August 5, 2008
Estradiol Julina Tablets 0.5 mg	Bayer Yakuhin, Ltd.	September 16, 2008
Mometasone Furoate Hydrate Nasonex Nasal Solution 50 µg 56 metered spray	Schering-Plough K.K.	September 16, 2008
Cetuximab (Genetical recombination) Erbitux Injection 100 mg	Merck Serono Co., Ltd.	September 19, 2008
Tazobactam-Piperacillin Hydrate ZOSYN	Taiho Pharmaceutical Co., Ltd.	October 1, 2008
Neostigmine Methylsulfate-Atropine Sulfate Hydrate Atvago Reverse Intravenous Injection Syringe 3 mL and 6 mL	Terumo Corporation	October 1, 2008
Rifabutin MYCOBUTIN Capsules 150 mg	Pfizer Japan Inc.	October 7, 2008
Ramosetron Hydrochloride Irribow Tablets 2.5 µg and 5 µg	Astellas Pharma Inc.	October 7, 2008
Pegaptanib Sodium MACUGEN IVT Inj. KIT 0.3 mg	Pfizer Japan Inc.	October 14, 2008
Interferon Alfa (NAMALWA) Sumiferon 300 and 600, Sumiferon DS 300 and 600 ^{*6}	Dainippon Sumitomo Pharma Co., Ltd.	October 16, 2008
Estradiol Julina Tablets 0.5 mg ^{*7}	Bayer Yakuhin, Ltd.	October 16, 2008
Freeze-dried Polyethylene Glycol Treated Human Normal Immunoglobulin kenketu glovenin-I-NICHIYAKU ^{*8}	Nihon Pharmaceutical Co., Ltd.	October 16, 2008

Ciclosporin ----- Neoral Oral Solution, Neoral Capsules 10 mg, 25 mg, and 50 mg ^{*9}	Novartis Pharma K.K.	October 16, 2008
Somatropin (Genetical Recombination) ----- Genotropin 5.3 mg, Genotropin MiniQuick s.c. inj. 0.6 mg, 1.0 mg, 1.4 mg, Genotropin Inj. 12 mg ^{*10}	Pfizer Japan Inc.	October 16, 2008
Bepidil Hydrochloride Hydrate ----- Bepricor Tablets 50 mg and 100 mg ^{*11}	Schering-Plough K.K.	October 16, 2008
Adapalene ----- Differin Gel 0.1%	Galderma Pharma S.A.	October 21, 2008
Tacrolimus Hydrate ----- Graceptor Capsules 0.5 mg, 1 mg, and 5 mg	Astellas Pharma Inc.	October 28, 2008

*1: Additional indications for “rheumatoid arthritis (including prevention for structural damage of joints), polyarticular-course juvenile idiopathic arthritis, and systemic-onset juvenile idiopathic arthritis”

*2: An additional indication for “prophylaxis of vein thromboembolism in patients undergoing abdominal surgery who are at risk for venous thromboembolism”

*3: An additional indication for “prophylaxis of thrombosis in patients with heparin-induced thrombocytopenia (HIT) type II”

*4: An additional indication for “reducing blood phenylalanine levels in patients with hyperphenylalaninemia (tetrahydrobiopterin-responsive hyperphenylalaninemia) due to tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency”

*5: An additional indication for “Paget disease of bone”

*6: An additional indication for “the improvement of viremia in compensated cirrhosis type C (except in the patients with HCV serogroup 1 and high blood HCV-RNA level)”

*7: An additional indication for “osteoporosis postmenopausal”

*8: An additional indication for “pemphigus (only for cases not adequately responsive to corticosteroids)”

*9: An additional indication for “dermatitis atopic (patients who are not adequately responsive to conventional therapies)”

*10: An additional indication for “SGA (Small-for-Gestational Age) dwarfism without epiphyseal closure”

*11: An additional indication for “sustained arterial fibrillation when other antiarrhythmic agents cannot be used or are ineffective”